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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/702,718	11/01/2000	Moon Jong Noh	55293.00003	9523

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EXAMINER	
WILSON, MICHAEL C	
ART UNIT	**PAPER NUMBER**
1632	12

DATE MAILED: 01/29/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/702,718	Applicant(s) Noh et al.
	Examiner Michael C. Wilson	Art Unit 1632

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *7-30-02 and 11-9-02*.

2a) ☒ This action is **FINAL.** 2b) ☐ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *2-5 and 13-15* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *2-5 and 13-15* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

The Art Unit location of your application in the USPTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Art Unit 1632.

Applicant's arguments filed 7-30-02, paper number 7, have been fully considered but they are not persuasive. The response filed 11-8-02, paper number 11, indicating a willingness to file a terminal disclaimer has been entered. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action. Claims 1, 6-12 and 16-22 have been canceled. Claims 2-5 and 13-15 are pending and under consideration in the instant application.

Specification

The objection to the amendment filed 10-9-01, paper number 6, under 35 U.S.C. 132 because it introduces new matter into the disclosure is withdrawn because the definition of what applicants consider "connective tissue" has been restored to the original definition.

Claim Objections

1. Claim 14 is objected to because of the following informalities: "...and DEAE-dextran..." should be --or DEAE-dextran--. Appropriate correction is required.

Claim Rejections - 35 USC § 112 - new matter

2. Claims 2-5 and 13-15 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The limitation of treating osteoarthritis with chondrocytes transfected with TGF-β1 or BMP is new matter (claim 13). Support has not been provided and cannot be found.

The phrase "transfected/transduced" is new matter. Support has not been provided and cannot be found (claims 4, 5 and 13).

Failure to provide support for future amendments will be considered non-responsive.

Claim Rejections - 35 USC § 112 - enablement

3. Claims 2-5 and 13-15 remain rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for transfecting chondrocytes with DNA encoding TGF-β1 operably linked to a promoter, transplanting the transfected chondrocytes into a joint space of a mammal such that expression of TGF-β1 occurs resulting in generating hyaline cartilage, does not reasonably provide enablement for using chondrocytes encoding BMP to regenerate hyaline cartilage as broadly claimed. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims for reasons of record.

The specific combination of vector, cell and modes of delivery required to target a desired tissue and regenerate tissue *in vivo* is unpredictable. Miller of record (1995, FASEB J., Vol. 9, pages 190-199) review the types of vectors available for *in vivo* gene therapy, and conclude that "for the long-term success as well as the widespread applicability of human gene therapy, there will have to be advances...targeting strategies outlined in this review, which are currently only at the experimental level, will have to be translated into components of safe and highly efficient delivery systems" (page 198, column 1). Deonarain of record (1998, Expert Opin. Ther. Pat., Vol. 8, pages 53-69) indicate that one of the biggest problems hampering successful gene therapy is the "ability to target a gene to a significant population of cells and express it at adequate levels for a long enough period of time" (page 53, first paragraph). Deonarain reviews new techniques under experimentation in the art which show promise but states that such techniques are even less efficient than viral gene delivery (see page 65, first paragraph under Conclusion section). Verma of record (Sept. 1997, Nature, Vol. 389, pages 239-242) reviews vectors known in the art for use in gene therapy and discusses problems associated with each type of vector. The teachings of Verma indicate a resolution to vector targeting has not been achieved in the art (see entire article). Verma also teaches appropriate regulatory elements may improve expression, but it is unpredictable what tissues such regulatory elements target (page 240, sentence bridging columns 2 and 3). Crystal of record (1995, Science, Vol. 270, page 404-410) also reviews various vectors known in the art and indicates that "among the design hurdles for all vectors are the need to

increase the efficiency of gene transfer, to increase target specificity and to enable the transferred gene to be regulated" (page 409).

More specifically, at the time of filing Naughton of record taught transplanting chondrocytes to a site of cartilage damage in the presence of scaffolding and regenerating cartilage, suggested transfecting the cells with a vector encoding TGF-β1 and suggested delivering the cells intraarticularly (claim 31; col. 10, line 58; col. 4, line 65; col. 13, line 60 - col. 16, line 33; col. 2, line 56 and col. 18, lines 8-42 which discusses administering the cells to joints that have damaged cartilage). Ikeda of record taught administering a vector encoding TGF-β1 intraarticularly to obtain TGF-β1 expression (pg 1667, col. 1, 3rd para.; pg 1669, col. 2). van Beuningen of record taught TGF-β1 administered intraarticularly generates articular cartilage (pg 307, col. 1, "intraarticular injections"; pg 308, col. 1, "stimulation of articular cartilage"). The art did not teach how to use BMP to regenerate hyaline cartilage.

The specification does not enable using chondrocytes transfected with DNA encoding BMP to generate hyaline cartilage. Specifically, the specification does not correlate the results obtained using TGF-β1 to BMP-2, -3, -4, -5, -6 or -7 such that cartilage would be regenerated. Nor does the specification correlate the function of TGF-β1 to BMP-2, -3, -4, -5, -6 or -7 such that cartilage could be regenerated. While the specification suggests using BMP (page 11, line 9), the activities and functions of TGF-β1 and BMPs vary. The specification does not provide the structural features or functional activity of any BMP required to regenerate cartilage or any other connective tissue. The specification does not correlate the results obtained using fibroblasts to

chondrocytes. The specification does not correlate the structure or function of fibroblasts and chondrocytes. Without such guidance, it would require one of skill undue experimentation to use different cells and DNA to regenerate connective tissue in view of the state of the art at the time of filing which only taught fibroblasts encoding TGF-β1.

Given the unpredictability in the art taken with the guidance provided in the specification, it would have required one of skill undue experimentation to use chondrocytes transfected with DNA encoding TGF-β1 or BMP to regenerate hyaline cartilage or any desired connective tissue as broadly claimed.

Applicants argue the specification suggests using chondrocytes and BMP on pg 5 and 9. Therefore, applicants believe the specification explicitly allows for the use of chondrocytes to regenerate cartilage following the same or similar method as using fibroblasts applying well known molecular biological techniques (pg 6 of response). Applicants argument is not persuasive. The rejection is not based on making transfected cells but how to use them to treat disease. Applicants have not provided any correlation between the results in the specification or the art at the time of filing and chondrocytes encoding TGF-β1 or BMP as claimed. Given the unpredictability of gene therapy taken with the teachings in the specification and the art regarding using chondrocytes encoding TGF-β1 and the lack of guidance regarding using BMP, one of skill in the art would not be able to extrapolate the results obtained using TGF-β1 to any BMP such that hyaline cartilage was regenerated.

Claim Rejections - 35 USC § 112 - indefiniteness

The rejection of claim 8 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention has been withdrawn because the claim has been canceled.

4. However, claims 2-5 and 13-15 as newly amended are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The phrase "transfected/transduced" is unclear. The metes and bound of "transfected" and "transduced" cannot be determined. Therefore, the metes and bounds of cells that are either "transfected" or "transduced" cannot be determined. The distinction between transfecting and transducing cannot be determined.

The phrase "chondrocyte cells" is indefinite. Chondrocytes are simply referred to as chondrocytes, not chondrocyte cells.

Claim Rejections - 35 USC § 102

The rejection of claims 16-21 under 35 U.S.C. 102(b) as anticipated by Agrawal (1995, Indian J. Exp. Biol., Vol. 33, pg 708-709) has been withdrawn because the claims have been canceled.

Claim Rejections - 35 USC § 103

The rejection of claims 16-22 under 35 U.S.C. 103(a) as being unpatentable over Agrawal (1995, Indian J. Exp. Biol., Vol. 33, pages 708-709) has been withdrawn because the claims have been canceled.

5. Claims 2-5 and 13-15 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Naughton (US Patent 5,842,477, Dec. 1, 1998) in view of Ikeda (Sept. 1998, J. Rheumatol., Vol. 25, pg 1666-1673) and van Beuningen (Sept. 1998, Osteoarthritis and Cartilage, Vol. 6, pg 306-317) for reasons of record.

Naughton taught transplanting chondrocytes to a site of cartilage damage in the presence of scaffolding and regenerating cartilage (claim 31; col. 10, line 58; col. 4, line 65). Naughton did not expressly teach transfecting the cells or administering the cells intraarticularly. However, Naughton suggested transfecting cells for transplant with a vector encoding TGF-β1 (column 13, line 60 - column 16, line 33) and delivering the cells intraarticularly (col. 2, line 56 and col. 18, lines 8-42 which discusses administering the cells to joints that have damaged cartilage). In addition, Ikeda taught administering a vector encoding TGF-β1 intraarticularly to obtain TGF-β1 expression (page 1667, column 1, 3rd paragraph; page 1669, column 2) and van Beuningen taught TGF-β1 administered intraarticularly generates articular cartilage (page 307, column 1, "intraarticular injections"; page 308, column 1, "stimulation of articular cartilage").

Thus, it would have been obvious to one of ordinary skill at the time the invention was made to make a vector encoding TGF-β1, transfect chondrocytes and administer the cells to the

joint of animal with cartilage damage such that cartilage repair is obtained. One of ordinary skill would have been motivated to deliver the chondrocytes intraarticularly to put the cells in contact with the joint as taught by Naughton. One of ordinary skill would have been motivated to transfect the chondrocytes with a vector encoding TGF-β1 to generate cartilage as taught by Ikeda and van Beuningen. The nomenclature of a vector is a non-effective variable routinely utilized by those of skill in the art; therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to name a vector taught by Naughton pmTβ1 (claim 15).

Applicants argue Naughton does not disclose injecting cells into the joint without scaffolding. Applicants argument is not persuasive because the claims are not limited to injecting cells into the joint without scaffolding. The combined teachings of Naughton, Ikeda and van Beuningen teach injecting chondrocytes transfected with a vector encoding TGF-β1 into the joint of a subject as claimed. The use of scaffolding in the method is encompassed by the claims.

Double Patenting

6. Claims 2-5 and 13-15 remain provisionally rejected under 35 U.S.C. 101 as claiming the same invention as that of claims 1-22 of copending Application No. 09/707900. This is a provisional double patenting rejection since the conflicting claims have not in fact been patented.

Applicants willingness to file a terminal disclaimer in the response filed 11-8-02, paper number 11, is noted.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

No claim is allowed.

Inquiry concerning this communication or earlier communications from the examiner should be directed to Michael C. Wilson who can normally be reached on Monday through Friday from 9:00 am to 5:30 pm at (703) 305-0120.

Questions of formal matters can be directed to the patent analyst, Tracey Johnson, who can normally be reached on Monday through Friday from 9:00 am to 5:30 pm at (703) 305-2982.

Questions of a general nature relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-1235.

If attempts to reach the examiner, patent analyst or Group receptionist are unsuccessful, the examiner's supervisor, Deborah Clark, can be reached on (703) 305-4051.

The official fax number for this Group is (703) 308-4242.

Michael C. Wilson

MICHAEL C. WILSON
PATENT EXAMINER